SUMMARY MINUTES

OF THE

IMMUNOLOGY DEVICES PANEL MEETING

OPEN SESSION

November 9, 1998

Conference Room 020B
9200 Corporate Blvd.
Rockville, Maryland

Immunology Devices Panel Meeting

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Panel Chairperson
Charles T. Ladoulis, M.D.

Executive Secretary
Louise E. Magruder

Voting Members
Betts Carpenter, M.D., Ph.D.
Henry A. Homburger, M.D.
Glen L. Hortin, M.D., Ph.D.
Mary M. Kemeny, M.D.
Gustavo Reynoso, M.D.
Sheila E. Taube, Ph.D.

Temporary Voting Members
Karen L. Kaul, M.D., Ph.D.
Worta McCaskill-Stevens, M.D.
Mary B. Todd, D.O.

Consumer Representative
Wilbert Jordan, M.D., M.P.H.

Industry Representative
Erika B. Ammirati, R.A.C.

National Cancer Institute
Edison T. Liu, M.D.

FDA Personnel
Larry E. Bockstahler, Ph.D.
OST/CDRH

Judy H. Chaio
Medical Officer, ODE/CDER

Peter E. Maxim, Ph.D.
Branch Chief, Immunology
DCLD/ODE/CDRH

Max Robinowitz, M.D.
Medical Officer, ODE, CDRH

Teng S. Weng, Ph.D.
Statistician
DBS/OSB/CDRH

Geretta Wood
Scientific Review, Immunology
DCLD/ODE/CDRH

NOVEMBER 9, 1998--OPEN PUBLIC SESSION

Panel Chair Charles T. Ladoulis, M.D., called the session to order at 10:30 a.m. The panel members introduced themselves and noted their areas of expertise. Panel Executive Secretary Louise E. Magruder gave a brief summary of the September 4, 1998 Joint Meeting of the Immunology Devices and Hematology and Pathology Devices Panels, at which the panel voted in favor of recommending for approval with conditions the premarket approval application (PMA) for DAKO Corporation's immunohistochemical assay to measure overexpression of HER2 to select patients for herceptin treatment. She noted 1999 panel dates of January 15, April 9, July 16, and October 15.

Max Robinowitz, M.D., Medical Officer in the Office of Device Evaluation (ODE), gave the panel an update on the Year 2000 date problem as it concerns computerized medical devices. He noted that many medical devices are subject to Year 2000 problems: these include microprocessor or personal computer (PC)-controlled products, medical device software applications, device interfaces to databases and recordkeeping, and embedded chips for date display or recording. Dr. Robinowitz defined the Year 2000 problem as failure of computer systems to properly process or display dates due to representing the year using only two digits or other date-related problems. He also read a definition of Year 2000 compliance, saying that a Year 2000 compliant-product is a product that is impervious to the date change.

Dr. Robinowitz noted that the FDA has a biomedical equipment database on its World Wide Web site that is continually updated and contains voluntary submission of

data provided by manufacturers. He gave the FDA web page address for the FDA product database, noting that information is posted there on Year 2000 compliance as it is received from manufacturers. It lists affected products and shows certification of all compliant products and those that do not use dates. The database shows that many companies have not yet reported. Most of those noncompliant products involve date stamping, which is a less serious issue, but a limited number have operational problems. Manufacturers are providing a variety of solutions.

Dr. Robinowtitz discussed the goals of the Y2K Information and Readiness Disclosure Act of October 1998. He reviewed current FDA/CDRH activities and requested panel assistance in three areas. These included advice regarding products in members' areas that could be affected, identification of types of products that could present actual patient risks, and suggestions regarding other actions to reduce risks. Advice could be sent to Panel Executive Secretary Louise Magruder. Dr. Robinowitz briefly listed future CDRH/FDA activities such as letters and guidances to manufacturers, expansion of the database, outreach/communications, action on products that present risks, and inspection al emphasis on Y2K. He listed issues for consideration on Y2K compliance in health care facilities.

Dr. Steven Gutman, Director of the Division of Clinical Laboratory Devices, thanked retiring panel members Drs. Reynoso and Jordan and presented them with a plaque.

Executive Secretary Louise Magruder read the conflict of interest statement and noted that waivers had been granted to Drs. Kaul and Ladoulis for their interest in firms potentially affected by the day's deliberations. Waivers are on file for Drs. Homburger

and Kemeny. The FDA had considered other past and current unrelated issues involving Drs. Kaul, McCaskill-Stevens, and Todd, and allowed them to participate fully. Ms. Magruder then read the appointment to temporary voting status for those three participants.

OPEN PUBLIC HEARING

Panel Chair Dr. Ladoulis invited public attendees to address the panel. There were no requests to speak.

A letter was read into the record from Dr. Philip Wyatt, Chief, Department of Genetics at North York General Hospital, in which he applauded the rapid response of the FDA in making available acceptable pharmaceutical and diagnostic treatments for breast cancer. He wrote to support the use of in situ hybridization in modern medical care and noted its availability and acceptance as part of a routine laboratory medicine. The Laboratory Proficiency Testing Program had made all laboratories in Ontario aware in 1996 that this is an expected laboratory medical practice and to clarify that all laboratories involved in modern cytogenetic and other genetic testing should use these techniques in patient care.

PREMARKET APPROVAL APPLICATION FOR P980024 PATHVYSION HER-2 DNA PROBE KIT BY VISIS, INC.

Sponsor Presentation

Dr. Russel Enns, a company employee, began the company presentation by describing the company profile and its typical products. He noted that in situ hybridization is a widely used technology, and he read the proposed intended use statement.

Dr. Dennis Slamon, who had no financial interests or stocks but whose way was paid by the company, described the dimensions of the health risk posed by breast cancer. He provided an overview of Human Epidermal Growth Factor Receptor-2 (HER-2/*neu*), noting that it is involved in the regulation of cell growth and its amplification or overexpression is associated with increased cell growth. Such amplification occurs in some 25-30% of breast cancers. He underlined its prognostic and predictive capabilities, saying that HER-2/*neu* alteration is associated with prognosis, and he showed data indicating its prognostic factor is second only to the number of nodes involved. It also serves as an indication of response to hormonal therapy; overexpression of HER-2 means patients will not respond well to tamoxifen. Patients with low HER-2/*neu* tend to get no added benefit from high-dose chemotherapy; patients with high HER-2/*neu* benefit from high-dose chemotherapy.

Dr. Steven Seelig, a company employee, discussed fluorescent in-situ hybridization (FISH) technology and reproducibility. He outlined FISH characteristics such as specimen versatility and its highly sensitive and specific nature. He also noted that the simple assay format requires a low level of interpretive skill, is quantitative, highly reproducible, and automatable, and uses equipment generally available in most laboratories. He explained the probe design and assay procedure, which included specimen preparation, hybridization, and microscopic examination and enumerations, and gave examples of microscopic images and probe verification.

Dr. Seelig summarized previous clearances of the same technology and explained Protocol 300 reproducibility results by assay-to-assay, observer-to-observer, site-to-site, and lot-to-lot comparisons. He also discussed portability of specimens between sites.

There were no statistically significant differences assay-to-assay, lot-to-lot, or day-to day. There were statistically significant but not important differences observer-to-observer and site-to-site. He concluded that the signal enumeration is precise at 20 nuclei, the assay is reliable and reproducible, and it provides accurate detection of amplification.

Dr. Donald Berry, an investigator under contract with no financial interest in the company and whose consulting fee was contributed to the study, discussed Protocol 302 and the Cancer and Leukemia Group B clinical utility trial 8869. He summarized the background and trial design, noting that the study was designed to determine whether a marker could be used to identify a subgroup more likely than other patients to benefit from high-dose chemotherapy. He concluded that the FISH test provides reliable detection of HER-2/*neu* amplification and that a significant dose-response effect exists for amplified HER-2/*neu* and CAF, but not in patients with little or no amplification. An association was found in DFS and OS that is consistent with HER-2/neu expression by IHC. The trial found no correlation between copy number, age, menopausal status, tumor size, and number of positive nodes. It found a significant negative correlation between copy number, ER and PR, and it showed the quality control methods were effective.

Dr. Slamon summarized FISH clinical utility and practicality. He listed the methods used for assessing HER-2/*neu* status in breast cancer and the FISH characteristics and gave his opinion that "the Vysis FISH test is the most reliable and accurate means of assessment of the HER-2/*neu* status in breast cancer tissue specimens."

Dr. Enns described the proposed training program, in which the laboratory will validate the PathVysion Kit by testing specimens with known amplification/overexpression for concordance with another reference test method. It will

test a minimum of 30 specimens including controls. The validation study must be conducted within 60 days of completion of training. A mandatory training program would report the results of the first 50 sites or six months to FDA. If the cumulative concordance is greater than or equal to 75% of reference method, the mandatory training program requirement could be dropped. Dr. Enns read the proposed intended use statement and reiterated the benefits and risks involved in rapid assessment of potential response to adjuvant therapy leading to choice of therapy.

FDA Presentation

Geretta Wood, Scientific Reviewer for Immunology in the DCLD, read the intended use statement and described the device. Preclinical studies were performed on hybridization efficiency, analytical sensitivity and specificity, stability, and repeatability. Clinical studies were done on reproducibility and clinical utility. Ms. Wood described the Protocol 300 reproducibility study objectives, noting that the study looked at a total of 120 paraffin-embedded tissue sections from four human breast carcinoma cell lines with known ratios of HER-2/*neu* to CEP 17s from three sites. No significant day-to-day or lot-to-lot variability was observed but site-to-site and observer-to-observer variability was noted. Ms. Wood discussed the Cancer and Leukemia Group B (CALGB) study 8541 which used archived samples to look at 1,572 women with node-positive, stage II breast cancer on chemotherapy. She described the companion study CALBG 8869, which investigated HER-2/*neu* expression by IHC, DNA index, s-phase fraction, and p53 accumulation. It showed a significant dose-response effect of adjuvant chemotherapy with CAF in patients with overexpression of HER-2/*neu*, but not in those with no overexpression.

Ms. Wood described the clinical study (Protocol 302). This study randomly selected tissue specimens from these studies to determine whether the amplification of HER-2/*neu,* as assessed by FISH with DNA probe, provides statistically significant and independent prognostic information on recurrence rate and disease-free and overall survival in stage II node-positive patients receiving adjuvant therapy. She reviewed the subject selection and exclusion criteria. Of the 524 subjects, 433 were HER-2/*neu* negative. The remaining positive samples were equally distributed among the three treatment arms of low, moderate, and high dose chemotherapy. Analysis with Cox proportional hazard model demonstrated a statistically significant dose-response effect of adjuvant chemotherapy with CAF in patients with amplified HER-2/*neu*, for both disease-free and overall survival.

Dr. Weng, an FDA statistician, gave a short statistical presentation on the subpopulation analysis performed by the FDA on the data available on the 524 patients in the Protocol 302 study. These patients were divided into those with less than or equal to 3 positive lymph nodes and more than or equal to four positive lymph nodes. This analysis looked at the statistical significance achieved within these groups when subdivided by HER-2/*neu* status and chemotherapy regimen.

Ms. Wood thanked the FDA review team and read the FDA questions to the panel for consideration.

OPEN COMMITTEE DISCUSSION

The panel discussion raised questions relating to the dose of adriamycin used, with the panel noting that the high dose used in this study is now considered standard treatment. Panel members also discussed the FISH versus immunohistochemical assays

and whether one assay might resolve discrepancies with others. It was noted that the sponsors recommend use of formalin-fixed samples.

In discussing the FDA questions, there was panel consensus that the data support the proposed intended use to detect amplification of the HER-2 gene accurately as defined by the sponsors. The panel had some discussion about whether knowledge of the HER-2/*neu* negative status offered any benefit in the management of patients with four or more positive nodes. They agreed on the wording that knowledge of the HER-2/*neu* negative status would offer benefit to any stage II, node-positive patient. They made no reference to the number of positive nodes because of lack of subset analysis.

The panel preferred to answer the question about HER-2/*neu* status offering an independent benefit in addition to node status in considering the use of high-dose therapy by redefining the intended use. They suggested a revised intended use that reads, "The PathVysion HER-2 DNA Probe Kit is designed to detect amplification of the HER-2/*neu* gene via fluorescence in situ hybridization (FISH) in paraffin-embedded specimens from subjects with lymph node positive and stage II breast cancer. Results from the PathVysion Kit are intended for use as a rapid assessment of the stage II lymph node positive patients for the potential response to adriamycin–containing adjuvant therapy. The testing will be performed in CLIA high-complexity laboratories."

On training programs, the panel was concerned over evaluation, interpretation, and performance of the test. They agreed that the training program needs to be that of a high-complexity assay like FISH and IHC that is designed for professional staff as well as for technologists to make sure the sample is appropriately and correctly analyzed. Some recommendations should be added to the package insert if not elsewhere with

references to professionally qualified staff (pathologists, etc.) overseeing the correct use of this test.

OPEN PUBLIC HEARING

There were no requests to address the panel.

The Panel Executive Secretary read the voting options to the panel.

A motion was made and seconded to recommend the PMA to the FDA for approval, subject to the following conditions: a) A prominent change should be made to the package insert to specify that a pathologist be involved in the selection and interpretation of tissue sections, assay preparation, and interpretation. b) The wording of the indication for use should be changed to read "stage II, lymph node positive patients" as given above. c) The wording should also be changed to "the potential response to adriamycin-containing therapy" as given in full above. d) The variability in performance of the assay is subject to FDA final approval based on an actual slide assay. e) A clear requirement should be spelled out in the package insert as to what specimens would be inappropriate due to insufficient fields of tumor sections, necrotic tissue, improper fixation, or improper handling.

The motion was carried unanimously.

On behalf of CDRH, the Executive Secretary thanked the panel, the sponsors, Dr. Liu, and the FDA staff.

The meeting was adjourned at 4:20 p.m.

I certify that I attended the Meeting of the Immunology Devices Panel on November 9, 1998, and that this summary accurately reflects what transpired.

Louise E. Magruder
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

Charles T. Ladoulis, M.D.
Panel Chair

Summary minutes prepared by
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